ACUTE TOXICITY SUMMARY

CHLORINE

(bertholite)

CAS Registry Number: 7782-50-5

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**210 µg/m³**
Critical effect(s)	throat irritation
Hazard Index target(s)	Respiratory System; Eyes

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	yellow/green gas
Molecular formula	Cl_2
Molecular weight	70.9
Density	2.9 g/L
Boiling point	-34.6°C
Melting point	-101°C
Vapor pressure	5 atm @ 10.3°C
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	slightly soluble in water
Odor threshold	0.2 ppm
Odor description	bleachy, pungent odor (Ruth, 1986)
Metabolites	N-chloro-derivatives of biomolecules; reacts with water to form hypochlorous acid, hydrochloric acid
Conversion factor	1 ppm = 2.9 mg/m³

Chlorine, although non-combustible by itself, reacts explosively with many chemicals including: acetylene, acetaldehyde, alcohols, alkyl isothiourea, salts, ammonia, benzene, t-butanol, carbon disulfide, diborane, diethyl ether, and glycerin.

III. Major Uses or Sources

Chlorine is used in the manufacture of rubber and plastics, pesticides, and other chlorinated hydrocarbons. It is also extensively used to bleach woodpulp and paper and is used as chlorinated lyme in the bleaching of all kinds of fabrics. It is used in the cleaning of dairy equipment and as a disinfectant in laundries and dishwater. It is also used in odor control and as a demulsifying agent in the treatment of water. When acid is mixed with household bleach (a dilute solution of sodium hypochlorite) in an attempt to increase the cleaning power of bleach, chlorine gas is released. Internationally, chlorine gas is the major source of toxic release incidents (Davis *et al*., 1989).

IV. Acute Toxicity to Humans

Chlorine exposure in the range of 3-6 ppm (9-17 mg/m^3) results in stinging or burning sensations from irritation and corrosion of mucous membranes including the eyes, skin, and the respiratory system (Baxter *et al*., 1989; Wither and Lees, 1985). In high concentrations, inhalation may result in necrosis of the tracheal and bronchial epithelium as well as in pulmonary edema. Delayed pulmonary edema may also develop up to 24 hours following acute exposure. Death at high exposure is mainly from respiratory failure or cardiac arrest due to toxic pulmonary edema. Bronchopneumonia may be a common and potentially lethal complication of pulmonary edema.

The odor threshold is not an adequate warning sign for overexposure to chlorine since the sense of smell rapidly accommodates at low concentrations, near the ACGIH 8-hour TLV of 0.5 ppm (1.45 mg/m^3) (Reprotext, 1999).

Anglen (1981) showed that exposure of "up to" 29 volunteer subjects to chlorine resulted in concentration- and time-dependent severity of irritation to the eyes and throat. In this study, volunteers were exposed for 4 or 8 hours to chlorine concentrations of 0, 0.5, 1.0, and 2.0 (4 hour exposures only) ppm. Severity of irritation was subjectively measured by questionnaires from the subjects every 15-60 minutes, and was divided into 5 categories, which ranged from barely perceptible to clearly objectionable. A consistent, statistically significant increase in throat irritation in subjects exposed to 1.0 ppm chlorine began at 1 hour into exposure. Consistent throat irritation was not observed in subjects during a 4-hour exposure to 0.5 ppm. However, 0.5 ppm chlorine produced throat irritation and an urge to cough after a 4-hour exposure (Anglen *et al*., 1980). A statistically significant decrease in group mean FEV_1 (-15.3%) was observed following 8-hour exposure to 1.0 ppm chlorine.

D'Alessandro *et al*. (1996) studied 10 subjects, five with and five without airway hyperresponsiveness (HR) after exposure to 1.0 ppm chlorine and five persons, all with HR, to 0.4 ppm chlorine for 1 hour by mouth-breathing facial mask. After inhalation of 1.0 ppm, there was a significant fall in FEV_1 immediately following exposure among both normal and HR subjects. The fall was greater among the HR subjects compared with the normals ($p = 0.04$). Specific airway resistance (SR_{aw}) increased to a greater degree among the HR group compared with normal subjects ($p = 0.04$). Among all 10 subjects, the proportional change in FEV_1 after exposure to 1.0 ppm chlorine correlated with baseline reactivity (Spearman rank correlation $r = 0.64$, $p < 0.05$). At 24-h follow-up, there were no significant chlorine-related pulmonary function deficits. After 0.4 ppm chlorine inhalation by the 5 persons with HR, there was no significant pulmonary function effect. These data indicated that persons with hyperreactive airways manifest a clinically significant, exaggerated airway response to chlorine at 1.0 ppm, but not at 0.4 ppm.

Rotman *et al*. (1983) studied clinically significant changes in pulmonary function tests (PFTs) following controlled chlorine exposures. Using a group of 9 volunteers (8 normal volunteers plus 1 volunteer with allergic rhinitis), data were collected on several PFTs following 4- and 8-hour exposures to 0, 0.5, and 1.0 ppm (0, 1.45, and 2.9 mg/m^3) chlorine. The subject with allergic rhinitis was excluded from the final group mean statistical analysis due to the severity of his response to chlorine exposure. Although 8-hour exposure to 1 ppm chlorine resulted in clinically

significant decreases in FEV_1 (4 subjects) and clinically significant increases in specific airway resistance (SR_{aw}) (4 subjects), there were no reports of respiratory distress among the normal subjects (Rotman *et al*., 1983; Rotman, 1994). The NOAEL for a clinically significant increase (100%) in SR_{aw} and clinically significant decrease (20%) in FEV_1 was 1 ppm for a 4-hour exposure.

The subject with allergic rhinitis developed shortness of breath and wheezing following 4-hour exposure to 1 ppm chlorine and left the exposure chamber due to development of shortness of breath and wheezing (Rotman *et al*., 1983). Pulmonary function tests showed that this subject had a clinically significant increase in pulmonary SR_{aw} and a clinically significant decrease in FEV_1 when compared to sham exposure of 8 healthy subjects and when compared to the subject's own sham control values. The subject also had compromised lung function relative to the 8 healthy subjects during sham exposures. The pulmonary tests under sham control conditions also showed that exposure of the sensitive subject to 0.5 ppm chlorine for 8 hours, but not 4 hours, resulted in a clinically significant, greater than 100% increase in SR_{aw} and clinically significant, greater than 20% decrease in FEV_1. However, no clinical symptoms and no apparent indication of bronchoconstriction were reported at this concentration.

The Rotman study is supported by two earlier human studies, which suggest that some test subjects develop respiratory distress at similar concentrations of chlorine. In a study by Rupp and Henschler (1967), the concentration of chlorine was gradually increased from 0 to 1.3 ppm over a 50 minute period. One subject developed shortness of breath and a severe headache following exposure to 1.0 to 1.3 ppm chlorine for 35 to 50 minutes. NIOSH (1976) suggested that this subject was sensitive to the irritant effects of chlorine. In a study by Beck (1959), 1 out of 10 subjects judged a 20 minute exposure to 1 ppm chlorine as unbearable due to sensory skin and conjunctival irritation, headache, and slight respiratory distress. It was not indicated in the study if this was a "sensitive" individual and it was unclear if clinical symptoms indicative of bronchoconstriction had actually occurred.

In another human exposure study, 6-8 healthy 'expert' volunteers (people familiar with irritant gases and laboratory exposure situations) easily tolerated exposure to 0.5, 1, and 2 ppm chlorine for 2 hours (Joosting and Verberk, 1975). Exposure of 3 expert volunteers to 4 ppm chlorine for 2 hours was considered a limit, due mainly to throat irritation. One of the 3 volunteers actually left the exposure chamber after 75 minutes, but it was unclear if this was due to throat irritation. However, no significant changes in ventilatory capacity (VC, FEV, and FIV) were noted at any concentration following exposure. The researchers considered 4 ppm to be unbearable for non-informed (non-expert) healthy subjects.

In a human poisoning case, a young male with a questionable history of asthma was exposed to 0.05 ounce/1,000 ft^3 ($^1/_{20}$ ounce per 1,000 cubic feet (equivalent to 19 ppm)) of chlorine for several minutes (Monto and Woodall, 1944). Immediately following exposure, the patient did not complain of any unusual irritation or shortness of breath. Several hours later, however, the subject was hospitalized with dyspnea and wheezing, with rales over the chest area. The diagnosis was pulmonary edema. The patient's past history included one questionable asthmatic attack in which he was subsequently told that he was sensitive to dust.

Predisposing Conditions for Chlorine Toxicity

Medical: Persons with skin, eye, respiratory, cardiovascular or neurologic conditions and smokers may be more sensitive to chlorine (Reprotext, 1999). Persons who are sensitive to irritants, such as those with RADS, may react strongly to chlorine.

Chemical: Smokers may be more sensitive to the effects of chlorine gas (Das and Blanc, 1993).

V. Acute Toxicity to Laboratory Animals

One of the most comprehensive acute lethality studies for chlorine was performed by Zwart and Woutersen (1988). Lethality data were collected for 4 exposure durations (5, 10, 30, and 60 minutes) in rats and 2 exposure durations (10 and 30 minutes) in mice. Clinical observations during exposure included restlessness, eye irritation, dyspnea, and nasal discharge. Nearly all rats that died during the course of the investigation did so during exposure or up to 1 week after exposure. However, many mice died during the second week post-exposure, which suggested that these delayed deaths were the result of secondary infection (Zwart and Woutersen, 1988). Post-mortem examination noted swollen lungs and increased lung weights in exposed rats and mice, indicative of pulmonary edema.

For studies that published adequate lethality data, the LC_{50}, MLE_{05} (maximum likelihood estimate corresponding to 5% lethality), BD_{05}, and BD_{01} (benchmark dose at the 95% lower confidence interval of the MLE_{05} and MLE_{01}, respectively) were determined by log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) and are shown in Table 1.

Table 1. Animal Lethality Benchmark Dose Determinations in ppm for Chlorine

Reference	Species	Exposure Time (min)	LC_{50} 60 min[1]	MLE_{05} 60 min[1]	BD_{05} 60 min[1]	BD_{01} 60 min[1]
MacEwen & Vernot, 1972	rat	60	294	233	197	169
	mouse	60	134	102	73	58
Zwart & Woutersen, 1988	rat	60	483	383	311	265
	mouse	30	285	164	-[2]	-[2]
	mouse	varied[3]	816	494	363	265
Schlagbauer & Hensc., 1967	mouse	30	105	76	54	43
Underhill, 1920	dog	30	500	228	111	66

[1] *Exposure time was extrapolated to 60 minutes using a modification of Haber's equation ($C^n * T = K$) where n = 2.8 for rats and 1.3 for mice.*

[2] *The 30 minute mouse lethality data were insufficient for benchmark dose determination.*

[3] *Lethality data for 2 durations (10 and 30 minutes) were pooled and normalized to a 1-hour exposure using the equation $C^n * T = K$, where n = 1.3.*

The values in Table 1 were extrapolated to equivalent 60-minute exposures, where needed, using a modification of Haber's equation, $C^n * T = K$. The exponent "n" was determined from the

lethality data provided by Zwart and Woutersen (1988) for each species by varying the term n in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) until the lowest chi-square value was achieved. The lethality data for chlorine indicate that the exponent is dependent on exposure duration ("n" increases with increasing exposure time). The rat data provide an n = 2.8 for extrapolation from 30 minute to 1 hour exposures. However, for exposures of 5-10 minutes in duration, the rat data indicate that n = 1 for extrapolation to 1-hour exposure. Extrapolation of the 10 and 30 minute mouse lethality data to 1-hour provides an n = 1.3.

The lethality data by Zwart and Woutersen (1988) probably provide the most accurate estimation of the BD_{05} for acute chlorine exposure. Inspection of the values in Table 1 suggests that mice are more sensitive to the lethal effects of chlorine. However, the 30-minute mouse data generated by the Zwart and Woutersen (1988) study were not usable for determining low dose lethality, as the variability of the dose-response slope was too high. By extrapolating the 10- and 30-minute mouse lethality data to 1-hour and pooling the values, a benchmark dose can be estimated from the mouse data (see Table 1). Calculating the BD_{05} by this method for mice results in a value similar to that determined for rats using data by the same authors.

Zwart and Woutersen (1988) determined lethality values higher than previous studies. However, the authors felt that the earlier studies were deficient, partly due to high fluctuations in chlorine concentration at each dose.

In other acute animal studies, a dose-response study for chlorine exposure in rabbits was performed by Barrow and Smith (1975). While the number of rabbits per group was not included in the report for all dose levels, a 30-minute LOAEL (500 ppm) and NOAEL (250 ppm) for lethality were determined. The study also identified a non-lethal, 30-minute LOAEL and NOAEL of 100 and 50 ppm, respectively, for severe pulmonary function changes and development of pulmonary edema.

Exposure of rats and mice to 9-11 ppm for 6 hours produced severe lesions in specific locations in both olfactory and respiratory epithelia of the nasal passages with a widespread loss of cilia (Jiang *et al*., 1983).

In order to develop an animal model of the asthma-like abnormality known as reactive airways dysfunction syndrome (RADS; acute, irritant-induced asthma), Demnati *et al*. (1995) evaluated the effects of exposure to various levels of chlorine on airway mucosa and lung parenchyma. Seventy-four Sprague-Dawley rats were exposed to air (controls) or to 50, 100, 200, 500, and 1,500 ppm of chlorine for 2 to 10 minutes. Histological assessment was performed at 1, 3, 6, 12, 24, and 72 hours after exposure. Exposure to 500 ppm did not induce significant histological changes. Exposure to 1,500 ppm for 2 minutes induced perivascular edema and the appearance of focal mild inflammation, whereas exposure to 1,500 ppm for 10 minutes caused profound histological changes, including airspace and interstitial edema associated with bronchial epithelial sloughing at 1 hour; decreased edema and the appearance of mucosal polymorphonuclear leukocytes at 6 to 24 hours (maximal at 12 hours); and epithelial regeneration, manifested by hyperplasia and goblet cell metaplasia, at 72 hours. Demnati *et al*. (1995) concluded that acute

exposure to chlorine at 1500 ppm for 10 minutes induces significant airway mucosal abnormalities that vary over a short period of time.

Winternitz et al. (1920) report severe lung edema and desquamation of the trachea and bronchial epithelium in dogs exposed to chlorine gas at lethal concentrations (concentration not reported). Bronchial constriction from the irritant properties was noted.

VI. Reproductive or Developmental Toxicity

No information is available on reproductive toxicity of chlorine in humans. Meier *et al*. (1985) determined that chlorine, predominantly in the form of hypochlorite, causes sperm head abnormalities when given in the drinking water at 4 mg/kg per day in mice. However, these effects were observed after three weeks exposure but were not present after five weeks.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects):

0.07 ppm (210 μg/m³)

Study	Anglen, 1981
Study population	29 adult volunteers
Exposure method	inhalation of 1.0 ppm chlorine for up to 8 hr
Critical effects	itching or burning of the throat
LOAEL	not determined
NOAEL	1 ppm
Exposure duration	30 minutes
Extrapolated 1 hour concentration	0.71 ppm (1^2ppm * 0.5 h = C^2 * 1 h) (see Table 12 for information on "n")
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	0.07 ppm (0.21 mg/m³; 210 μg/m³)

A published value of 3.5 for "n" is based on animal lethality data for chlorine (Ten Berge *et al*., 1986). However, in this case, a value of 2 for "n" appears to be more appropriate based on graphic representation of the human throat irritation data in the Anglen study.

Level Protective Against Severe Adverse Effects

In the D'Alessandro *et al*. (1996) study, after inhalation of 1.0 ppm chlorine for 1 hour, there was a significant fall in FEV_1 among subjects with hyperreactive airways. After 0.4 ppm chlorine inhalation by the 5 persons with hyperreactive airways, there was no significant effect on pulmonary function. The data indicated that persons with hyperreactive airways, a sensitive

subpopulation, manifest a clinically significant, exaggerated airway response to chlorine at 1.0 ppm, but not at 0.4 ppm. Since the exposure was for 1 hour in a sensitive population, no time adjustment or uncertainty factor is applied. Thus 0.4 ppm (1.2 mg/m^3) is a level protective against severe adverse effects for chlorine. (The sensitive individual in the study by Rotman *et al*. (1983) and less reliable evidence for respiratory distress in sensitive individuals from 3 other studies (Rupp and Henschler, 1967; Beck, 1959; Monto and Woodall, 1940) resulted in a severe adverse effect level of 1 ppm after time extrapolation from 4 hours to 1 hour. The D'Alessandro *et al*. (1996) study tested sensitive subjects. The overall uncertainty was lower, thus it was selected as the key study.)

Level Protective Against Life-threatening Effects

The comprehensive chlorine lethality study conducted in rats and mice by Zwart and Woutersen (1988) provides the best data for estimation of the life threatening level. The results suggested that the "n" for the equation $C^n \times T = K$ is dependent on exposure duration. However, the 1-hour lethality data for rats were sufficient for determining a BD_{05}. Data from earlier lethality studies in the literature (see Table 1) produced lower LD_{50}s and BDs than those produced by Zwart and Woutersen (1988). The researchers felt that continuous monitoring of the chlorine gas concentration to keep the concentration extremely stable during exposure produced higher, but more accurate, values. Based on probit analysis of the data, a BC_{05} of 311 ppm was determined in rats for 1-hour exposure to chlorine. Uncertainty factors of 3 to account for interspecies differences and 10 to account for the increased susceptibility of sensitive human individuals were applied to the BC_{05}.

$$\text{level protective against life-threatening effects} = BC_{05}/(UF)$$

The total uncertainty factor was 30. Incorporation of these factors resulted in a level protective against life-threatening effects of 10 ppm (29 mg/m^3) for 1-hour exposure to chlorine.

NIOSH (1995) reports a (revised) IDLH for chlorine of 10 ppm based on acute inhalation toxicity data in humans.

VIII. References

Anglen DM. Sensory response of human subjects to chlorine in air [PhD dissertation]. Ann Arbor (MI): University Microfilms International; 1981.

Anglen DM, Smith RG, Byers DH, Hecker LH. Sensory response of human subjects to low levels of chlorine in air [abstract 159]. American Industrial Hygiene Conference Abstracts. May 27-June 1, 1980. Chicago (IL). 1980. p. 92.

Barrow RE, Smith RG. Chlorine-induced pulmonary function changes in rabbits. Am Ind Hyg Assoc J 1975;36:398-403.

Baxter PJ, Davies PC, Murray V. Medical planning for toxic releases into the community: the example of chlorine gas. Br J Ind Med 1989;46:277-285.

Beck H. Experimental determination of the olfactory thresholds of some important irritant gases (chlorine, sulfur dioxide, ozone, nitrous gases) and symptoms induced in humans by low concentrations. Inaugural Dissertation. Wuerzburg, Germany: Julius-Maximilians-Universität, 1959. p. 1-12.

Crump K. A new method for determining allowable daily intakes. Fundam Appl Toxicol 1984;4:860-866.

Crump KS, Howe R. Probit-A computer program to extrapolate quantile animal toxicological data to low doses. Ruston (LA): KS Crump & Company, Inc.; 1983.

D'Alessandro A, Kuschner W, Wong H, Boushey HA, Blanc PD. Exaggerated responses to chlorine inhalation among persons with nonspecific airway hyperreactivity. Chest 1996;109(2):331-337.

Das R, Blanc PD. Chlorine gas exposure and the lung: a review. Toxicol Ind Health 1993;9(3):439-455.

Davis DS, DeWolf GB, Ferland KA, *et al*. Accidental releases of air toxics: prevention, control, and mitigation. Park Ridge (NJ): Noyes Data Corp; 1989. p. 6-9. [cited in Das and Blanc, 1993.]

Demnati R, Fraser R, Plaa G, Malo JL. Histopathological effects of acute exposure to chlorine gas on Sprague-Dawley rat lungs. J Environ Pathol Toxicol Oncol 1995;14(1):15-19.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (CD-ROM version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

Jiang KZ, Buckley LA, Morgan KT. Pathology of toxic responses to the RD50 concentration of chlorine gas in the nasal passages of rats and mice. Toxicol Appl Pharmacol 1983;71:225-236.

Joosting PE, Verberk MM. Emergency population exposure: a methodical approach (with a report on a human experiment with chlorine). In: Proceedings International Symposium. Recent advances in the assessment of the health effects of environmental pollution. Paris, 24-28 June 1974. Vol. 4. Luxembourg: CEC; 1975. p. 2005-2029.

MacEwen J, Vernot E. Annual Technical Report: AMRL-TR-72-62 (NTIS AD755-358). Wright-Patterson Air Force Base (OH): Aerospace Medical Research Laboratory, Toxic Hazards Research Unit; 1972.

Meier JR, Bull RJ, Stober JA, Cimino MC. Evaluation of chemicals used for drinking water disinfection for production of chromosomal damage and sperm-head abnormalities in mice. Environ Mutagen 1985;7(2):201-211.

Monto RW, Woodall PS. Mediastinal emphysema resulting from exposure to a pulmonary irritant. War Med 1944;6:251-252.

(NIOSH) National Institute for Occupational Safety and Health. Criteria for a recommended standard...Occupational exposure to chlorine. DHEW Pub. NIOSH 76-170. Cincinnati: NIOSH; 1976.

(NIOSH) National Institute for Occupational Safety and Health. Chemical listing and documentation of revised IDLH (as of March 1, 1995). Available at http://www.cdc.gov/niosh/intridl4.html.

Reprotext® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Rotman HH, Fliegelman MJ, Moore T, Smith RG, Anglen DM, Kowalski CJ, *et al*. Effects of low concentrations of chlorine on pulmonary function in humans. J Appl Physiol 1983;54(4):1120-1124.

Rotman HH. Written communication. 1994.

Rupp H, Henschler D. Wirkungen geringer Chlor- und Bromkonzentrationen auf den Menschen. Int Arch Gewerbepathol Gewerbehyg 1967;23:79-90.

Ruth J. Odor thresholds and irritation levels of several chemical substances: A review. Am Ind Hyg Assoc J 1986;47:142-151.

Schlagbauer M, Henschler D. Toxicitat von Chlor und Brom bei einmaliger und wiederholter Inhalation. Int Arch Gewerbepathol Gewerbehyg 1967;23:91-98.

Ten Berge WF, Zwart A, Appelman LM. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J Hazard Mater 1986;13:301-309.

Underhill FP. The use of lethal war gases. The lethal war gases, physiology and experimental treatment. New Haven (CT): Yale University Press; 1920. Chapters 1 and 2. p. 1-8 and 183-192.

Winternitz MC, Lambert RA, Jackson L, Smith GH. The pathology of chlorine poisoning. In: Collected Studies on the Pathology of War Gas Poisoning. MC Winternitz, ed. New haven: Yale University Press,1920.

Withers RMJ, Lees FP. The assessment of major hazards: the lethal toxicity of chlorine. Part 1. Review of information on toxicity. J Hazard Mater 1985;12:231-282.

Zwart A, Woutersen RA. Acute inhalation toxicity of chlorine in rats and mice: time-concentration-mortality relationships and effects on respiration. J Hazard Mater 1988;19(2):195-208.